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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/557, 31/47, 31/415, A61P 15/10 // (A61K 31/557, 31:47, 31:415)		A1	(11) International Publication Number: WO 00/15233 (43) International Publication Date: 23 March 2000 (23.03.00)
(21) International Application Number: PCT/US99/21513 (22) International Filing Date: 17 September 1999 (17.09.99) (30) Priority Data: 09/154,677 17 September 1998 (17.09.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/154,677 (CIP) Filed on 17 September 1998 (17.09.98) (71) Applicant (for all designated States except US): ZONAGEN, INC. [US/US]; B-4, 2408 Timberloch Place, The Woodlands, TX 77380 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): PODOLSKI, Joseph, S. [US/US]; 3 Pebble Hollow Court, The Woodlands, TX 77381 (US). (74) Agent: UHL, Jill, E.; Marshall, O'Toole, Gerstein, Murray & Borun, 6300 Sears Tower, 233 South Wacker Drive, Chicago, IL 60606 (US).			(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMPOSITIONS FOR THE TREATMENT OF MALE ERECTILE DYSFUNCTION			
(57) Abstract Improved drug compositions and methods useful in the treatment of male erectile dysfunction. An optimized mixture of the drugs phentolamine mesylate, papaverine hydrochloride, and alprostadil in a buffer containing L-arginine and glycine is to be injected into the penile tissue to produce an erection in otherwise impotent men.			

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COMPOSITIONS FOR THE TREATMENT OF MALE ERECTILE DYSFUNCTION

BACKGROUND OF THE INVENTION

5 This invention relates to improved drug compositions useful in the treatment of male erectile dysfunction and also to methods of treatment. More particularly, this invention discloses specific formulations comprising one or more of the following pharmaceutically active agents: an α -adrenergic antagonist, a phosphodiesterase inhibitor and a prostaglandin in a novel buffer and the administration of such formulations to mammals (including
10 humans) to treat erectile dysfunction.

Erectile dysfunction is a common medical disorder affecting about 20 million men in the U.S. alone. Male erectile dysfunction has been defined as the inability to achieve or maintain an erection sufficient for intercourse (*Impotence*, National Institutes of Health Consensus
15 Development Panel on Impotence Conference, JAMA 1993, 270, 83-90). The dominant etiology for this condition is arterial insufficiency associated with cardiovascular disease. Male erectile dysfunction adversely impacts the quality of life, being frequently associated with depression, anxiety, and low self-esteem. Although male erectile dysfunction represents a major clinical
20 problem, treatment for this condition remains problematic and unsatisfactory.

One of the least invasive therapies available entails the use of a vacuum constriction device on the penis to produce an erection. The physiology of the penis is such that blood flows in through arteries deep within the tissue while blood flows out through veins near the skin surface.
25 By placing a plastic cylinder over the shaft of the penis and employing a vacuum pump to restrict venous blood flow from the penis, the corpus cavernosum penile tissue becomes engorged with trapped blood and an erection is produced. Common patient complaints are that this device is interruptive to the sex act, has a short duration of effectiveness, and can
30 cause tissue damage to the penis, such as necrosis, with extended use.

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Penile prosthesis implantation is an alternative treatment of
erectile dysfunction. This therapy entails surgically implanting a mechanical
device inside the penis (for example see U.S. Pat. No. 5,065,744 to
Zumanowshky). This device can be a semi-rigid malleable rod or a fluid
5 inflated tube which can be operated by the patient to achieve an erection.
Although this method does not affect the ability to urinate, ejaculate, or have
an orgasm, the surgery required to implant the prosthesis can lead to pain,
infection, and scarring.

Recent insights into the physiological mechanism of penile
10 erection have led to the development of other therapies for the treatment of
erectile dysfunction. Preliminary studies have shown that during sexual
arousal, nitric oxide molecules are released into the surrounding tissue from
nerve endings and endothelial cells in the genitals. These nitric oxide
molecules then cause the enzyme guanylate cyclase to produce cyclic
15 guanosine monophosphate (cGMP) which lowers the level of intracellular
calcium in the surrounding medium and allows for the relaxation of smooth
muscle cells. In the penis, the relaxation of the corpus cavernosal smooth
muscle cells permits increased blood flow into the cavernosal spaces which
leads to greater intracavernosal pressure thereby producing penile rigidity.

20 It follows then that a pharmacological agent which inhibits the
breakdown of cGMP would have the potential to prolong or enhance the
erectile response during sexual stimulation. The drug sildenafil (ViagraTM,
Pfizer, Inc.) is one such pharmacological agent which, when given orally, has
shown some success in this manner (Terrett, N.K. et al. Bioorg. Med. Chem.
25 Lett. 1996, 6, 1819-1824).

Other types of oral therapies which are available to treat erectile
dysfunction by different means include centrally-acting drugs such as
atipamezole (Farnos Orion) which is an α -adrenergic antagonist,
apomorphine (Pentech Pharmaceuticals) which is a dopaminergic agonist,
30 Sildenafil (Pfizer, Inc.) which is a phosphodiesterase inhibitor, and

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phentolamine formulations (VasomaxTM, Zonagen) which are also α -adrenergic antagonists/vasodilators. This family of drugs appears to act by expanding arteries and relaxing penile tissue (smooth muscle cells) which, in combination, entraps blood in the penis thereby producing an erection.

5 However, some oral therapies may have drawbacks with respect to efficacy and side effects. Therefore, in those cases it would be beneficial to treat erectile dysfunction or to enhance erectile ability directly by administering medicaments directly on/into the penis itself. These modes of administration may also minimize the dosage of the medicament needed.

10 One alternative route for administering vasoactive agents like those mentioned above is by transdermal administration to the penis. The compound alprostadil (prostaglandin E1) is formulated as a cream (Macrochem) which is absorbed into the penile tissue. Alprostadil has been shown to bind to specific receptors in penile tissue which is accompanied by
15 an increase in cellular cyclic adenosine monophosphate (cAMP) levels. The physiological mechanism, as described with cGMP above, results in a decrease in intracellular calcium in the cytoplasm and the relaxation of smooth muscle cells. These vasodilatory effects result in rapid arterial inflow and expansion of the sinusoidal spaces within the penis. This action then
20 restricts venous outflow from the penis whereby penile rigidity develops. Another vasoactive agent, papaverine hydrochloride, is formulated into a patch (PharmaPatch, Pharmedia) to be applied to the skin of the penis and acts as a non-specific phosphodiesterase inhibitor to maintain cGMP levels in a similar sort of mechanism as described above which produces an erection.
25 These external treatments of the skin surface of the penis suffer from the drawback that the sex partner comes into contact with the drug during intercourse and can be adversely affected.

The above-mentioned pharmacological agents and routes of administration represent therapies for the treatment of erectile dysfunction
30 which can be successful for about 75-80% of the 20 million men having

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erectile dysfunction. However, for the remaining 20-25%, a different treatment is needed which often includes intraurethral and/or intracavernosal injection therapy.

Currently, there are two FDA-approved injection therapies —
5 available (Caverject®, Pharmacia-Upjohn; and Edex™, Schwartz Pharma),
both of which employ alprostadil as the active component. Caverject® is
commercially marketed as a freeze-dried powder containing the active
ingredient alprostadil in a base of lactose, sodium citrate, and benzyl alcohol.
When reconstituted with water, Caverject® is injected into the intracavernosal
10 space of the penis. Similarly, EDEX™ is a lyophilized powder containing
alprostadil, α -cyclodextrin, and anhydrous lactose. It is also reconstituted
with water before injection into the intracavernosal space of the penis. A
urethral suppository of alprostadil (MUSE™, Vivus, Inc.) has also recently
been introduced into the market; however, it has shown disappointing clinical
15 results (Biotech. Newswatch, June 15, 1998, 4-5). Not all men suffering from
erectile dysfunction respond to alprostadil therapy alone.

In order to treat these individuals who were non-responsive to
alprostadil, Zorngiotti et al. (J. Urol. 133:39-41 (1985), incorporated herein by
reference) demonstrated that the intracavernosal injection of a combination of
20 papaverine hydrochloride and phentolamine mesylate rapidly produced
transitory penile tumescence which could be followed by an erection in
response to sexual stimulation.

Similarly, Althof et al. (J. Sex Marital Ther. 17(2):101-112
(1991), incorporated herein by reference) reported that intracavernosal
25 injection of papaverine hydrochloride and phentolamine mesylate resulted in
improved erectile ability in about 84% of patients injected. However, there
was a high dropout rate (57%) in this study because 25% of patients
developed fibrotic nodules, 30% had abnormal liver functions, and 19%
experienced bruising of the penile tissue. In another study using the same
30 combination of phentolamine mesylate and papaverine hydrochloride, the

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intracavernous injection of this combination led to marked penile fibrosis in the patients injected (see Larsen, E.K. et al. J. Urol. 137, 292-293 (1987) incorporated herein by reference).

Therefore, a need exists for a safe and effective alternative treatment for erectile dysfunction which minimizes the drawbacks of the therapies described above to those currently available.

SUMMARY OF THE INVENTION

Compositions and methods for the treatment of male erectile dysfunction are provided. When injected into the corpus cavernosum, the compositions of this invention aid in producing, enhancing, or sustaining an erection of the penis. The compositions comprise one or more of an α -adrenergic antagonist, a prostaglandin and optionally a phosphodiesterase inhibitor. Preferred α -adrenergic antagonists include phentolamine mesylate and phentolamine hydrochloride as well as other pharmaceutically acceptable salts of phentolamine. Preferred phosphodiesterase inhibitors include papaverine hydrochloride. Class V phosphodiesterase inhibitors such as Sildenafil (Pfizer), for example, are more preferred. Alprostadil is a preferred prostaglandin. Any pharmaceutically acceptable salts, hydrates, hemihydrates, esters or other pharmaceutically acceptable forms of the foregoing pharmaceutically active agents are also included within the scope of the invention. The compositions of the invention may further comprise a buffer wherein the buffer comprises one or more substrates for nitric oxide synthetase.

One embodiment of the invention comprises phentolamine mesylate, alprostadil and papaverine hydrochloride (Trimix). Preferably, the trimix further comprises a buffer wherein the buffer comprises one or more substrates for nitric oxide synthetase. Preferred buffers comprise glycine, arginine and mixtures thereof. Even more preferably, the buffer comprises a mixture of glycine, L-arginine, mannitol, and benzyl alcohol in water which, when combined with the active ingredients, results in an injectable mixture

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with a pH of about 6 - 8. Another embodiment comprises phentolamine mesylate and alprostadil. Preferably, this embodiment further comprises the above described buffers.

Any of the foregoing buffers may also comprise other
5 pharmaceutical excipients, carriers and the like. One advantage of using the buffers of the invention in conjunction with the active agents described above is the resulting improved solubility profiles of the pharmaceutically active agents. Additionally, the buffers provide substrates for the enzyme nitric
10 oxide synthetase, which has been shown to play a role in the erectile response, and may result in a lower dosage requirement for efficacy.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to improved compositions which, by way of a non-limiting example, comprise one or more of the vasoactive agents phentolamine mesylate, papaverine hydrochloride, and
15 alprostadil (or any pharmaceutically acceptable salts of these vasoactive agents). Another aspect of the invention is directed to compositions comprising one or more vasoactive agents such as papaverine, phentolamine, and alprostadil in a buffer comprising glycine, L-arginine, or a mixture of glycine and L-arginine. By virtue of the improved solubility profiles
20 of the vasoactive agents in the buffers of the present invention, the use of the inventive compositions lowers the incidence of fibrotic nodules in the penis and priapism caused by precipitation and depot formation of vasoactive agents at the site of injection. Without being bound by theory, it is also believed that the presence of L-arginine or other substrates for nitric oxide
25 synthetase in the compositions of the invention may lower the dosage of the active agents required to effectively treat erectile dysfunction.

The invention is illustrated with reference to phentolamine as the α -adrenergic antagonist and in particular, with reference to phentolamine mesylate or phentolamine hydrochloride. Phentolamine can exist in solvated
30 as well as unsolvated forms, including hydrated forms, e.g., hemi-hydrate. In

general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for the purposes of the invention. Phentolamine can also form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrohamic acids such as hydrochloric and hydrobromic; as well as other acids such as sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, toluenesulfonic, and other mineral and carboxylic acids known to those skilled in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for the purposes of this invention.

When compositions according to the present invention comprise only an α -adrenergic antagonist or a phosphodiesterase inhibitor or a prostaglandin as the pharmaceutically active agent, the composition will further comprise a buffer which buffer comprises a substrate for nitric oxide synthetase such as arginine. When the compositions of the invention comprise two or more of the pharmaceutically active agents described above, the compositions optionally comprise buffers which comprise a substrate for nitric oxide synthetase.

One exemplary embodiment is a composition comprising an α -adrenergic antagonist (e.g., phentolamine mesylate), a phosphodiesterase inhibitor (e.g., papaverine hydrochloride or Sildenafil), and a prostaglandin (e.g., alprostadil) in a buffer. The active ingredients phentolamine mesylate, papaverine hydrochloride, and alprostadil are present in the composition in a weight ratio in the range of about 0.1:1.0:0.001 to about 5:30:0.02. Preferably,

the weight ratio of phentolamine mesylate: papaverine hydrochloride: alprostadil is about 1:30:0.01. More preferably, the weight ratio of phentolamine mesylate: papaverine hydrochloride: alprostadil is about 5:7.5:0.005.

5 Dosages of the vasoactive components of the invention are in the range of about 0-40 µg/ml alprostadil, about 0-50 mg/ml papaverine, and about 0-10 mg/ml phentolamine in a total volume of about 0.5 ml. Preferred dosages of the inventive compositions are in the range of about 1-5 mg/ml phentolamine, about 0-30 mg/ml papaverine, and about 5-20 µg/ml
10 alprostadil in a total volume of about 0.5 ml. More preferably, the dose is about 5 mg/ml phentolamine, about 7.5 mg/ml papaverine, and about 0.005 mg/ml alprostadil in a total volume of about 0.5 ml.

 Another exemplary embodiment is a composition comprising, an α-adrenergic antagonist (e.g., phentolamine mesylate), and a prostaglandin
15 (e.g., alprostadil) optionally in a buffer. The active ingredients, phentolamine mesylate and alprostadil are present in the composition in a weight ratio in the range of about 0.1:0.001 to about 5:0.02. Preferably the weight ratio of phentolamine mesylate: alprostadil is about 5:0.005.

 Dosages of the vasoactive components of the invention in this
20 embodiment are in the range of about 0-40 µg/ml alprostadil and about 0-10 mg/ml phentolamine in a total volume of about 0.5 ml. Preferred dosages are in the range of about 1-5 mg/ml phentolamine and 5-20 µg/ml alprostadil in a total volume of about 0.5 ml. More preferably, the dose is about 5 mg phentolamine and about 0.005 mg/ml alprostadil in a total volume of about
25 0.5 ml.

 In the case of a composition of the invention containing only phentolamine as the vasoactive agent in combination with a buffer such as an arginine and/or glycine containing buffer, the preferred dosage is about 1.25 mg/ml in a total volume of 0.5 ml. For a composition containing only
30 papaverine as the vasoactive agent in combination with an arginine and/or glycine containing buffer, the preferred dosage is about 7.5 mg/ml in a total

volume of 0.5 ml. In a composition containing only alprostadil as the vasoactive agent in an arginine and/or glycine containing buffer, the preferred dosage is about 5 µg/ml in a total volume of 0.5 ml. Compositions comprising only two of the vasoactive agents in a buffer according to the present invention are also contemplated by the invention.

The active ingredients are administered in a buffer which enhances their solubility and/or provides a substrate for nitric oxide synthetase. The buffer preferably contains glycine, mannitol, and benzyl alcohol in water. In this buffer, the content of glycine is preferably in the range of about 1% to about 2% by weight. More preferably, the buffer contains L-arginine, glycine, and other pharmaceutically acceptable excipients such as mannitol, and benzyl alcohol in water. The weight ratio of L-arginine to glycine in this preferred buffer is about 1:20. The pH of the composition in buffer is from about 3 to about 9. A preferred pH range for the composition in buffer is from about 6 to about 8. A neutral pH is the most preferable.

Also included in the present invention is a method for the treatment of male erectile dysfunction which comprises administering a pharmacologically effective amount of a composition comprising one or more of an α -adrenergic antagonist, a phosphodiesterase inhibitor, and a prostaglandin. Preferably, in this method the composition comprises phentolamine mesylate, papaverine hydrochloride, and alprostadil in a buffer. In this method of treatment, the route of administration is a member of the group consisting of oral, transdermal, subcutaneous intraperitoneal, intramuscular, and intrapenile (including intracavernosal). A preferred route of administration is by intracavernosal injection.

One composition utilized in this method of treatment preferably comprises phentolamine mesylate, papaverine hydrochloride, and alprostadil in a weight ratio in the range of about 0.1:0.0:0.001 to about 5:30:0.02. Preferably, phentolamine mesylate, papaverine hydrochloride, and alprostadil are present in the composition in a weight ratio of about 1:30:0.01. More

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preferably, phentolamine mesylate, papaverine hydrochloride, and alprostadil are present in the composition in a weight ratio of about 0.5:7.5:0.005.

Dosages of the vasoactive agents useful in this method of treatment are in the range of about 0-40 µg/ml alprostadil, about 0-50 mg/ml papaverine, and about 0-10 mg/ml phentolamine in a total volume of about 0.5 ml. Preferred dosages of the vasoactive agents are in the range of about 1-5 mg/ml phentolamine, about 0-30 mg/ml papaverine, and about 5-20 µg/ml alprostadil in a total volume of about 0.5 ml. More preferably, the dose used in this method is about 5 mg/ml phentolamine, about 7.5 mg/ml papaverine, and about 0.005 mg/ml alprostadil in a total volume of about 0.5 ml.

In methods utilizing a composition containing only phentolamine as the vasoactive agent, the preferred dosage rate is about 1.25 mg/ml in a total volume of 0.5 ml. In methods utilizing a composition containing only papaverine as the vasoactive agent, the preferred dosage rate is about 7.5 mg/ml in a total volume of 0.5 ml. In methods using a composition containing only alprostadil as the vasoactive agent, the preferred dosage rate is about 5 µg/ml in a total volume of 0.5 ml.

Another composition utilized in this method comprises an α-andrenergic antagonist (e.g., phentolamine mesylate), and a prostaglandin (e.g., alprostadil). The active ingredients, phentolamine mesylate and alprostadil are present in the composition in a weight ratio in the range of about 0.1:0.001 to about 5:0.02. Preferably the weight ratio of phentolamine mesylate: alprostadil is about 5:0.005.

Dosages of the vasoactive components of the invention are in the range of about 0-40 µg/ml alprostadil and about 0-10 mg/ml phentolamine in a total volume of about 0.5 ml. Preferred dosages are in the range of about 1-5 mg/ml phentolamine and 5-20 µg/ml alprostadil in a total volume of about 0.5 ml. More preferably, the dose is about 5 mg phentolamine and about 0.005 mg/ml alprostadil in a total volume of about 0.5 ml.

The buffer used to solubilize the active ingredients in the foregoing methods comprise mixtures of glycine, mannitol, and benzyl alcohol

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in water. The glycine content of this buffer is preferably in the range of about 1% to about 2% by weight. More preferably, the buffer comprises a mixture of glycine, L-arginine, mannitol, and benzyl alcohol in water. The weight ratio of glycine to L-arginine in the preferred buffer is about 1:20. The pH of the composition of the invention in the buffer is from about 3 to about 9. A preferred pH range for the composition in buffer is from about 6 to about 8. A neutral pH is most preferable.

The invention is also directed to a unit dosage form of any of the compositions described herein.

The present invention is further illustrated by the following examples. Example 1 describes an experiment designed to assess the increased solubility of the active ingredients, phentolamine, papaverine, and alprostadil, in a buffer comprising glycine and arginine. Example 2 demonstrates the ability of the improved compositions to induce penile erection in rabbits upon the intracavernosal injection of the composition containing phentolamine mesylate, papaverine hydrochloride, and alprostadil in buffer at various pH. Example 3 describes how the improved compositions of the present invention can be used for the treatment of erectile dysfunction in humans. Example 4 demonstrates the safety and efficacy of the improved compositions when used to treat erectile dysfunction in humans.

The foregoing specification and Examples are intended to illustrate the present invention and are not intended to limit the scope of the invention as set out in the appended claims.

EXAMPLE 1

Solubility of Phentolamine-Papaverine in Glycine-Arginine Buffer

Papaverine is sparingly soluble (<1 mg/ml) in the presence of phentolamine at physiological pH. Under these conditions papaverine may precipitate producing a deposit of solid drug at the injection site. This deposit of solid papaverine could act as a depot of drug which continues to exert its

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effects on erectile ability over time increasing the risk for priapism and the occurrence of nodules/fibrosis in the penis.

In order to address this problem, the buffers comprising glycine, arginine, or a mixture of glycine and L-arginine were prepared in an attempt to promote the solubility of the active ingredients papaverine and phentolamine and to provide a substrate for nitric oxide synthetase. A series of saturated solutions containing the pharmaceutically active ingredients in buffer at various pH were prepared, filtered, then analyzed by a high performance liquid chromatograph (HPLC) with an ultra-violet wavelength detector to determine the concentration of the dissolved phentolamine and papaverine active ingredients.

Saturated solutions of papaverine hydrochloride and solid phentolamine mesylate at a constant ratio of about 6 to about 1 were added in the amounts indicated in Table 1 to buffer containing about 0.1 M glycine and about 2 mM L-arginine, initial pH 8.2. A 0.1 N solution of NaOH was used to adjust the pH to the indicated values. These solutions were shaken for about 10 minutes and held at room temperature overnight in order to allow maximum dissolution of drugs in the buffer. The samples were then filtered through a 0.45 μ PFTE filter to remove undissolved drug and analyzed by HPLC to determine how much of each drug went into solution at the various pH values. HPLC was performed using a C18 column having a mobile phase of buffer (5 mM NaH_2PO_4 and 5 mM octane sulfonic acid, pH 3) in 30% acetonitrile with a flow rate of 1.5 ml/minute. The detection wavelength was 210 nm. Standard curves of both phentolamine and papaverine were prepared and the concentration of the phentolamine-papaverine mixtures in the samples was determined by measurement of peak area. The results are shown in Table 1 below.

Table 1Solubility of active agents in buffer

	<u>pH</u>	<u>Papaverine (mg/ml)</u>		<u>Phentolamine (mg/ml)</u>	
		<u>Added to Buffer</u>	<u>In Solution</u>	<u>Added to Buffer</u>	<u>In Solution</u>
5	3.91	66	36.81	11	12.12
	4.35	60	7.75	10	9.88
	5.04	60	0.7	10	6.5
	7.48	60	0.17	10	4.97
	7.65	60	0.2	10	6.99

10 The data demonstrates that for papaverine the solubility was about 36.81 g/ml in the glycine-arginine buffer at pH 3.91. In contrast, in a glycine-arginine buffer of pH 7.48, the solubility was only about 0.2 mg/ml . Therefore, the use of a buffer containing glycine and L-arginine at a pH of about 3-5 enhances the solubility of papaverine in contrast to a buffer having a pH greater than 7.0. Similarly, the solubility of phentolamine in the mixture

15 was, in general, greater at lower pH. However, at pH 7.65 an increase in solubility of phentolamine was seen. The increased solubility of the vasoactive drugs in the buffers of the present invention reduces the possibility that the drugs will form depots at the site of injection.

EXAMPLE 2**Intracavernosal Injection of Trimix Formulations**

Four New Zealand white rabbits were utilized in this study to determine the effects of the intracavernosal injection of two formulations of the compositions of the present invention. The compositions comprised a trimix of alprostadil, phentolamine mesylate and papaverine hydrochloride. The detailed compositions are listed in Table 2 below. The content of formulations A and B is similar except that formulation B contains no L-arginine.

Table 2**Composition of Injectable Trimix Formulations**

	<u>Formulation A (per ml)</u>	<u>Formulation B (per ml)</u>
Alprostadil	20 µg	20 µg
Phentolamine Mesylate	5 mg	5 mg
Papaverine HCl	30 mg	30 mg
L-Arginine	0.35 mg	None
Glycine	7.5 mg	7.5 mg
Mannitol	24 mg	24 mg
Benzyl alcohol	8.4 mg	8.4 mg
	Final pH: 3.98	Final pH: 4.01
	Sterile filtered	Sterile filtered

Two of the rabbits underwent intracavernosal injections of solution A and the other two rabbits underwent intracavernosal injections of solution B. In preparation for these injections, the rabbits were anesthetized by intramuscular injection of ketamine (35 mg/kg) and xylazine (5 mg/kg). Anesthesia was maintained with 0.2 ml intravenous bolus injections of pentobarbital (25 mg/ml) as needed. A 20 gauge angiocatheter was placed into the carotid artery for on-line measurement of systemic arterial pressure.

A 23 gauge mini-catheter was placed intracavernosally for measurement of intracavernosal pressure during erection. Baseline arterial blood pressure and intracavernosal pressure were recorded. Once baseline had been established, 0.2 ml of either solution A or solution B was injected intracavernosally. The effects of intracavernosal drug administration on intracavernosal pressure and systemic arterial pressure were continuously recorded. Further intracavernosal injections were made if full penile erection was not produced.

The results indicate that the first rabbit given an intracavernosal injection of 0.2 ml of solution A experienced a full penile erection lasting more than 30 minutes. The intracavernosal pressure, a measurement of engorgement, increased from about 30 mm Hg to about 63 mm Hg (91% of mean systemic arterial pressure after injection). The only side effect noted was a minor hypotension event lasting for approximately 10 seconds. There was no effect on heart rate.

The second rabbit given an intracavernosal injection of 0.2 ml of solution A also experienced a full penile erection lasting about 4 minutes. The intracavernosal pressure after injection rose from about 35 mm Hg to about 69 mm Hg (83% of mean systemic arterial pressure). This rabbit was injected intracavernosally a second time with 0.2 ml of solution A which produced another full penile erection lasting more than 30 minutes. After the second intracavernosal injection, the intracavernosal pressure increased from about 45 mm to about 81 mm Hg (96% of mean systemic arterial pressure). The only side effect noted was a minor transient hypotension which lasted for about 8 seconds. There was no effect on heart rate.

The third rabbit received an intracavernosal injection of 0.2 ml of solution B which produced a partial erection lasting for 3 minutes. The first injection increased intracavernosal pressure from about 36 mm Hg to about 50 mm Hg (60% of mean systemic arterial pressure). The second injection produced a full penile erection lasting for over 30 minutes. After the second intracavernosal injection, intracavernosal pressure increased from about 28

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mm Hg to about 65 mm Hg (96% of mean systemic arterial pressure). The only side effect noted was a minor transient hypotension lasting for approximately 6 seconds. There was no effect on heart rate.

5 The fourth rabbit received two injections, each 0.2 ml of solution B, which failed to produce an erection and caused only a minor increase in intracavernosal pressure from about 15 mm Hg to about 33 mm Hg. A third injection of 0.2 ml of solution B produced a partial erection increasing intracavernosal pressure from about 30 mm Hg to about 45 mm Hg (64% of mean systemic arterial pressure). A fourth injection of 0.2 ml of solution B
10 caused a full penile erection lasting for about 15 minutes. After the fourth injection the intracavernosal pressure increased from 42 mm Hg to about 65 mm Hg (88% of systemic arterial pressure). After every injection a transient minor hypotension lasting for 5-8 seconds was observed. There was no change in heart rate.

15 These experiments demonstrate that the intracavernosal administration of solution A or solution B produced penile erection in the rabbit. Erectile response to solution A occurred after one injection in the first rabbit and after two injections in the second animal. Erectile response to solution B occurred after two injections in the first animal and after four
20 injections in the second animal. Therefore, it appears that both solutions A and B containing the active ingredients phentolamine mesylate, papaverine hydrochloride, and alprostadil in buffers of either glycine or glycine-arginine provide effective treatment of male erectile dysfunction; however, fewer injections were required to produce an erection in rabbits using solution A.
25 Solution A containing L-arginine, as well as glycine, appears therefore to be more effective as an erectile dysfunction therapy than solution B.

EXAMPLE 3**Treatment of Erectile dysfunction in Humans**

Although the foregoing examples describe the effect of a trimix of alprostadil, phentolamine mesylate, and papaverine hydrochloride in buffers with or without arginine on erectile function in rabbits, these compositions are also useful for the treatment of erectile dysfunction in humans. The proper dose of active agents for administration to humans may be readily determined by one of ordinary skill in the art. For example, appropriate base-line dosages may be determined by reference to Zorngiotti, et al. (J. Urol. 133:39-41, 1985) who demonstrated that intracavernosal injection of 30 mg of papaverine in combination with 0.5 to 1 mg phentolamine (total volume of one ml) produced penile erection in response to sexual stimulation.

Dosages of the active agents useful in the compositions and methods of the present invention are in the range of about 0 to about 40 µg/ml alprostadil, about 0 to about 50 mg/ml papaverine, and about 0 to about 10 mg/ml phentolamine in a total volume of about 0.5 ml. Preferred dosages of the inventive compositions are in the range of about 1-5 mg/ml phentolamine, about 7.5-30 mg/ml papaverine, and about 5-20 µg/ml alprostadil in a total volume of about 0.5 ml. More preferably, the dose of the inventive compositions is about 5 mg/ml phentolamine, about 7.5 mg/ml papaverine, and about 0.005 mg/ml alprostadil in a total volume of about 0.5 ml. Erectile response may be measured by any of several criteria well known in the art.

According to the invention, the use of arginine or other substrates for nitric oxide synthesis in combination with vasoactive substances including phentolamine and/or alprostadil and/or papaverine may enhance or restore sexual response or responsiveness in men suffering from erectile dysfunction when compared to the composition without arginine or other nitric acid synthetase substrates. The presence of arginine or other nitric oxide synthetase substrates may also allow the use of smaller dosages

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of the vasoactive agents resulting in a more cost-effective therapy, with fewer side effects.

EXAMPLE 4

Intracavernosal Injection Study in Humans

5 A randomized, double-blind, placebo controlled study was designed to compare the pharmacodynamics and safety of the following Trimix formulations.

	<u>Trimix 1</u>	<u>Trimix 2</u>
Prostaglandin E1	0.01 mg	0.005 mg
Phentolamine Mesylate	1.0 mg	5.0 mg
10 Papaverine HCl	30.0 mg	7.5 mg
L-Arginine	0.35 mg	0.35 mg
Glycine	7.5 mg	7.5 mg
Mannitol	24 mg	24 mg
Benzyl Alcohol	8.4 mg	8.4 mg
15 Final pH	4.01	4.01

65 male patients who failed oral treatment each received the following treatment combinations over the 4 week duration of the study.

	<u>TREATMENT</u>	<u>PAPAVERINE</u> <u>DOSE (mg)</u>	<u>PHENTOLAMINE</u> <u>DOSE (mg)</u>	<u>ALPROSTADIL</u> <u>DOSE (mg)</u>
	1 (placebo)	0	0	0
20	2 (Caverject)	0	0	0.02
	3 (Trimix 1)	30	1	0.01
	4 (Trimix 2)	7.5	5	0.005

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The treatment sequence order in which each patient was dosed was randomized and double blind with each patient receiving one dose of blinded treatment combination each week.

5 The study medication was administered by injection of 0.5 ml into the corpus cavernosum through the dorsal aspect of the penis using a 26 or 27 gauge insulin type needle. Each patient completed a self-assessment of erectile response at 0, 5, 10, 20, 30, 45, 60, 75, 90 and 120 minutes after injection. The results were as follows:

10	<u>TREATMENT COMBINATION</u>	<u>PATIENTS ACHIEVING FULL ERECTIONS (n=65)</u>	<u>EFFICACY (%)</u>
	1	0	0
	2	17	26%
	3	22	34%
	4	27	42%

15 As the phentolamine concentration increased, the efficacy of the composition also increased. Efficacy is defined as the % of patients able to achieve a full erection following the injection. These data are surprising because phentolamine injected by itself only results in tumescence and not in full erection.

20 In summary, these data demonstrate that patient's who fail at initial oral therapy or other injection therapy can benefit from the improved formulations described herein. However, the formulation and methods of the invention may also be used as a first course of treatment for erectile dysfunction. The foregoing specification is intended to illustrate the present invention but is not intended to limit the invention as set out in the appended claims. Still other variations within the spirit and scope of the present invention are possible and will readily present themselves to those skilled in the art.

WE CLAIM:

1. A composition comprising one or more pharmaceutical agents selected from the group consisting of an α -adrenergic antagonist, a prostaglandin and optionally, a phosphodiesterase inhibitor.
2. A composition comprising one or more pharmaceutical agents selected from the group consisting of an α -adrenergic antagonist, a prostaglandin, and optionally, a phosphodiesterase inhibitor in a buffer wherein said buffer comprises a substrate for nitric oxide synthetase.
3. The composition of claim 1 or 2 wherein the α -adrenergic antagonist is phentolamine mesylate, or a pharmaceutically acceptable salt thereof.
4. The composition of claim 1 or 2 wherein the phosphodiesterase inhibitor is selected from the group consisting of papaverine hydrochloride, Sildenafil, class V phosphodiesterase inhibitors, and pharmaceutically acceptable salts thereof.
5. The composition of claim 3 wherein the phosphodiesterase inhibitor is selected from the group consisting of papaverine hydrochloride, Sildenafil, class V phosphodiesterase inhibitors, and pharmaceutically acceptable salts thereof.
6. The composition of claim 1 or 2 wherein the prostaglandin is alprostadil.
7. The composition of claim 3 wherein the prostaglandin is alprostadil.

8. The composition of claim 5 wherein the prostaglandin is alprostadiol.
9. The composition of claim 2, 5, 7 or 8 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.
10. The composition of claim 3 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.
11. The composition of claim 4 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.
12. The composition of claim 6 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.
13. The composition of claims 2, 5, 7 or 8 wherein the buffer comprises glycine having a pH range of from about 3 to about 5.
14. The composition of claim 3 wherein the buffer comprises glycine having a pH range of from about 3 to about 5.
15. The composition of claim 4 wherein the buffer comprises glycine having a pH range of from about 3 to about 5.
16. The composition of claim 6 wherein the buffer comprises glycine having a pH range of from about 3 to about 5.
17. The composition of claim 1, 2, 5, 7 or 8 wherein the buffer comprises a mixture of arginine and glycine having a pH range of from about 3 to about 5.

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18. The composition of claim 3 wherein the buffer comprises a mixture of arginine and glycine having a pH range of from about 3 to about 5.

19. The composition of claim 15 or 16 wherein the buffer comprises a mixture of arginine and glycine having a pH range of from about 3 to about 5.

20. The composition of claim 13 wherein the buffer comprises a mixture of arginine and glycine having a pH range of from about 3 to about 5.

21. The composition of claim 17 wherein the buffer comprises glycine and L-arginine in a weight ratio of about 1:20.

22. The composition of claim 18 wherein the buffer comprises a glycine and L-arginine in a weight ratio of about 1:20.

23. The composition of claim 16 or 18 wherein the buffer further comprises benzyl alcohol and mannitol and has a pH range of from about 3 to about 5.

24. The composition of claim 17 wherein the buffer further comprises benzyl alcohol and mannitol and has a pH range of from about 3 to about 5.

25. A composition comprising a combination of phentolamine mesylate, alprostadil and optionally, papaverine hydrochloride in a buffer wherein said buffer comprises a substrate for nitric oxide synthetase.

26. The composition of claim 25 wherein the weight ratio of phentolamine mesylate: papaverine hydrochloride: alprostadil is about 0.5:7.5:0.005 to about 5:30:0.02.

27. The composition of claim 26 wherein the weight ratio of phentolamine mesylate : papaverine hydrochloride: alprostadil is about 5:7.5:0.005.

28. The composition of claim 25 wherein the dosage of phentolamine mesylate, papaverine hydrochloride, and alprostadil are from about 0-10 mg/ml phentolamine, about 0-50 mg/ml papaverine, and about 0-40 µg/ml alprostadil.

29. The composition of claim 28 wherein the dosage of phentolamine mesylate, papaverine hydrochloride, and alprostadil are from about 1-5 mg/ml phentolamine, about 7.5-30 mg/ml papaverine, and about 5-20 µg/ml alprostadil.

30. The composition of claim 29 wherein the dosages of phentolamine mesylate, papaverine hydrochloride, and alprostadil are about 5 mg/ml phentolamine, about 7.5 mg/ml papaverine, and about 0.005 mg/ml alprostadil.

31. The composition of claims 28-30 wherein the vasoactive agents are present in a total volume of 0.5 ml.

32. The composition of claim 25 wherein the dosage of alprostadil is about 5 µg/ml in a total volume of 0.5 ml.

33. The composition of claim 25 wherein the dosage of phentolamine is about 1.25 mg/ml in a total volume of 0.5 ml.

34. The composition of claim 25 wherein the pH range of the composition in buffer is from about 3 to about 9.

35. The composition of claim 34 wherein the pH of the composition in buffer is about 7. —

36. A method for the treatment of male erectile dysfunction which comprises administering a pharmacologically effective amount of a composition comprising one or more pharmaceutical agents selected from the group consisting of an α -adrenergic antagonist, a prostaglandin and optionally, a phosphodiesterase inhibitor.

37. A method for the treatment of male erectile dysfunction which comprises administering a pharmacologically effective amount of a composition comprising one or more pharmaceutical agents selected from the group consisting of an α -adrenergic antagonist, a prostaglandin and optionally, a phosphodiesterase inhibitor in a buffer wherein said buffer comprises a substrate for nitric oxide synthetase.

38. The method of claim 36 or 37 wherein the α -adrenergic antagonist is phentolamine mesylate, or pharmaceutically acceptable salt thereof.

39. The method of claim 36 or 37 wherein the phosphodiesterase inhibitor is papaverine hydrochloride or pharmaceutically acceptable salt thereof.

40. The method of claim 38 wherein the phosphodiesterase inhibitor is papaverine hydrochloride or pharmaceutically acceptable salt thereof.

41. The method of claim 36, 37 or 40 wherein the prostaglandin is alprostadil.
42. The method of claim 38 wherein the prostaglandin is alprostadil.
43. The method of claims 36, 37, 40 or 42 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.
44. The method of claim 38 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.
45. The method of claim 39 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.
46. The method of claim 41 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.
47. The method of claim 43 wherein the buffer comprises glycine having a pH range of from about 3 to about 5.
48. The method of claims 44-46 wherein the buffer comprises glycine having a pH range of from about 3 to about 5.
49. The method of claim 47 wherein the buffer comprises a mixture of arginine and glycine having a pH range of from about 3 to about 5.
50. The method of claim 48 wherein the buffer comprises a mixture of arginine and glycine having a pH range of from about 3 to about 5.

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51. The method of claim 49 or 50 wherein the buffer comprises glycine and L-arginine in a weight ratio of about 1:20.

52. The method of claim 49 wherein the buffer further comprises benzyl alcohol and mannitol and has a pH range of from about 3 to about 5.

53. The method of claim 37 wherein the pH of the composition in buffer is about 7.

54. A method for the treatment of male erectile dysfunction which comprises administering a pharmacologically effective amount of a composition comprising one or more of phentolamine mesylate, alprostadil, and optionally, papaverine hydrochloride in a buffer wherein said buffer comprises a substrate for nitric oxide synthetase.

55. The method of claim 50 wherein the weight ratio of phentolamine mesylate: papaverine hydrochloride: alprostadil is about 0.5:7.5:0.005 to about 5:30:0.02.

56. The method of claim 55 wherein the weight ratio of phentolamine mesylate: papaverine hydrochloride: alprostadil is about 5:7.5:0.005.

57. The method of claim 54 wherein the dosage of phentolamine mesylate, papaverine hydrochloride, and alprostadil are about 0-10 mg/ml phentolamine, about 0-50 mg/ml papaverine, and about 0-40 µg/ml alprostadil.

58. The method of claim 57 wherein the dosage of phentolamine mesylate, papaverine hydrochloride, and alprostadil are about

1-5 mg/ml phentolamine, about 7.5-30 mg/ml papaverine, and about 5-20 µg/ml alprostadil.

59. The method of claim 58 wherein the dosages of phentolamine mesylate, papaverine hydrochloride, and alprostadil are about 5 mg/ml phentolamine, about 7.5 mg/ml papaverine, and about 0.005 mg/ml alprostadil.

60. The method of claims 57, 58 or 59 wherein the vasoactive agents are present in a total volume of 0.5 ml.

61. The method of claims 54 wherein the dosage of alprostadil is about 5 µg/ml in a total volume of 0.5 ml.

62. The method of claims 54 wherein the dosage of phentolamine is about 1.25 mg/ml in a total volume of 0.5 ml.

63. The method of claim 54 wherein the pH range of the composition in buffer is from about 3 to about 9.

64. The method of claim 63 wherein the pH of the composition in buffer is about 7.

65. A composition comprising an α -adrenergic antagonist, a prostaglandin and optionally a phosphodiesterase inhibitor in a pharmaceutically acceptable carrier or excipient.

66. The composition of claim 65 wherein the α -adrenergic antagonist is phentolamine or a pharmaceutically acceptable salt thereof.

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67. The composition of claim 65 or 66 wherein the phosphodiesterase inhibitor is selected from the group consisting of papaverine hydrochloride, Sildenafil, class V phosphodiesterase inhibitors, and a pharmaceutically acceptable salt thereof.
68. The composition of claim 65 or 66 wherein the prostaglandin is alprostadil.
69. The composition of claim 67 wherein the prostaglandin is alprostadil.
70. The composition according to claims 65, 66 or 67 further comprising a buffer.
71. The composition of claim 67 further comprises a buffer.
72. The composition of claim 68 further comprises a buffer.
73. The composition according to claim 78 wherein the buffer comprises glycine, arginine, or a mixture thereof.
74. The composition according to claim 71 or 72 wherein the buffer comprises glycine, arginine, or a mixture thereof.
75. The composition according to claim 73 wherein the composition in buffer has a pH range from about 3 to about 9.
76. The composition according to claim 74 wherein the composition in buffer has a pH range from about 3 to about 9.

77. The composition according to claim 75 or 76 wherein the pH of the composition in buffer is about 7.

78. The use of one or more pharmaceutical agents selected from the group consisting of an α -adrenergic antagonist, a prostaglandin and optionally a phosphodiesterase inhibitor for the manufacture of a medicament for the treatment of erectile dysfunction wherein one or more of said agents are in a buffer comprising a substrate for nitric oxide synthetase.

79. The use of claim 78 wherein the α -adrenergic antagonist is phentolamine mesylate, or pharmaceutically acceptable salt thereof.

80. The use of claim 78 or 79 wherein the phosphodiesterase inhibitor is selected from the group consisting of papaverine hydrochloride, Sildenafil, class V phosphodiesterase inhibitors, and a pharmaceutically acceptable salt thereof.

81. The use of claim 78 or 79 wherein the prostaglandin is alprostadil.

82. The use of claim 80 wherein the prostaglandin is alprostadil.

83. The use of claims 78, 79 or 82 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.

84. The use of claim 80 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.

85. The use of claim 81 wherein the buffer comprises L-arginine and, optionally, a pharmaceutically acceptable excipient or carrier.

86. The use of claim 78, 79 or 82 wherein the buffer comprises glycine having a pH range of from about 3 to about 5.

87. The use of claim 80 when the buffer comprises glycine having a pH range of from about 3 to about 5.

88. The use of claim 81 wherein the buffer comprises glycine having a pH range of from about 3 to about 5.

89. The use of claim 78, 79 or 82 wherein the buffer comprises a mixture of arginine and glycine having a pH range of from about 3 to about 5.

90. The use of claim 80 wherein the buffer comprises a mixture of arginine and glycine having a pH range of from about 3 to about 5.

91. The use of claim 81 wherein the buffer comprises a mixture of arginine and glycine having a pH range of from about 3 to about 5.

92. The use of claim 89 wherein the buffer comprises glycine and L-arginine in a weight ratio of about 1:20.

93. The use of claim 90 or 91 wherein the buffer comprises glycine and L-arginine in a weight ratio of about 1:20.

94. The use of claim 89 wherein the buffer further comprises benzyl alcohol and mannitol and has a pH range of from about 3 to about 5.

95. The use of claim 90 wherein the buffer further comprises benzyl alcohol and mannitol and has a pH range of from about 3 to about 5.

96. The use of claim 78 wherein the composition in buffer has a pH of about 7.

97. The use of a composition comprising a combination of phentolamine mesylate, alprostadil and optionally, papaverine hydrochloride in a buffer for the manufacture of a medicament wherein said buffer comprises a substrate for nitric oxide synthetase.

98. The use of claim 97 wherein the weight ratio of phentolamine mesylate: papaverine hydrochloride: alprostadil is about 0.5:7.5:0.005 to about 5:30:02.

99. The use of claim 98 wherein the weight ratio of phentolamine mesylate: papaverine hydrochloride: alprostadil is about 5:7.5:0.005.

100. The use of claim 97 wherein the dosage of phentolamine mesylate, papaverine hydrochloride, and alprostadil are about 0-10 mg/ml phentolamine, about 0-50 mg/ml papaverine, and about 0-40 μ g/ml alprostadil.

101. The use of claim 100 wherein the dosage of phentolamine mesylate, papaverine hydrochloride, and alprostadil are about 1-5 mg/ml phentolamine, about 7.5-30 mg/ml papaverine, and about 5-20 μ g/ml alprostadil.

102. The use of claim 93 wherein the dosage of phentolamine mesylate, papaverine hydrochloride, and alprostadil are about 5 mg/ml

phentolamine mesylate, about 7.5 mg/ml papaverine hydrochloride, and about 0.005 mg/ml alprostadil.

103. The use of claims 100, 101 or 102 wherein the vasoactive agents are present in a total volume of 0.5 ml.

104. The use of claim 97 wherein the dosage of alprostadil is about 5 μ g/ml in a total volume of 0.5 ml.

105. The use of claim 97 or 104 wherein the dosage of phentolamine is about 1.25 mg/ml in a total volume of 0.5 ml.

106. The use of claim 97 wherein the pH range of the composition in buffer is from about 3 to about 9.

107. The use of claim 106 wherein the pH of the composition in buffer is about 7.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/21513

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/557 A61K31/47 A61K31/415 A61P15/10
 //(A61K31/557,31:47,31:415)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHAO, R AND CLOWERS, D E: "Experience with Intracavernosal Tri-Mixture for the Management of Neurogenic Erectile Dysfunction" ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION, vol. 75, no. 3, 1994, pages 276-278, XP002125438 abstract Materials and Methods Table 1 Discussion <div style="text-align: center;"> <div>---</div> <div>---/---</div> </div>	1-107



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search

13 December 1999

Date of mailing of the international search report

30/12/1999

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INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/US 99/21513

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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X	<p>TRUSS, M.C. ET AL.: "Intracavernous pharmacotherapy"</p> <p>WORLD JOURNAL OF UROLOGY, vol. 15, 1997, pages 71-77, XP002125440</p> <p>Summary page 72, column 1, paragraph 3 -page 73, column 1, paragraph 4 page 73, column 2, line 16 - line 24</p>	1-107
X	<p>WO 90 02545 A (AMSU LTD ;HAGGREN JOHAN (SE)) 22 March 1990 (1990-03-22)</p> <p>abstract page 4, last paragraph -page 5, paragraph 3 table I claims 1-51</p>	1-107
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P,X	<p>WO 98 52569 A (PODOLSKI JOSEPH S ;ZONAGEN INC (US)) 26 November 1998 (1998-11-26)</p> <p>abstract page 1, line 12 -page 5, line 23 page 6, line 11 -page 9, line 22 examples 1,3 claims 1-19</p>	1-107
A	<p>WO 97 33597 A (BJELDBAK GITTE) 18 September 1997 (1997-09-18)</p> <p>the whole document</p>	1-107

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